For The United States Patent and Trademark Office

Applicants:	P. Bertelsen et al.
Application no.:	09/786,864
National Filing Date:	10 July 2001
For:	Quick release pharmaceutical compositions of drug substances
Examiner:	Pulliam, Amy E
Art unit:	1615

DECLARATION OF POUL BERTELSEN

1. I, **Poul Bertelsen**, of Copenhagen, Denmark, one of the named inventors of the above-captioned patent application do state and declare as follows:

2. I believe that I am a person skilled in the art to which the above-captioned application pertains. I am a Senior Research Scientist within the field of Pharmaceutical Development and have 15 years working experience with the formulation of pharmaceuticals.

3. I have read and understood the pending claims in the application in question, the first Office Action related thereto, dated 23 September 2002, and the cited prior art (Masami et al). In respect to the first Office Action, I have the following comments:

4. It is my understanding that Masami et al describes a method for improving the dissolution of NSAIDs in gastric fluid by including an alkaline substance in the composition.

5. I wish to remark that it is my further understanding that such alkaline-containing compositions of Masami et al are manufactured by a process including a conventional granulation step (see embodiments 1-8 of Masami et al).

6. According to pharmaceutical textbooks, the term "granulation" relates to a process for treating powders so as to make the powder more suitable for being compressed into tablets. During the granulation process, smaller particles are gathered together into larger, permanent "aggregates" that may be termed granules. See enclosed copy of reference, pharmaceutical Dosage Forms: Tablets volume 1, Marcel Dekker, Inc., Edited by Herbert A. Lieberman, Leon Lachman and Joseph B. Schwartz, 1989, page 148.

7. According to Masami et al, the particle size of the granules may pass a sieve of 20 Mesh or less (see page 5, last sentences of the translated application). I wish to remark that particles that passes a sieve of 20 Mesh relates to

particles with a particle size of less than about 800 µm. Thus, compositions of Masami et al is based on particulate compositions with a particle size of less than 800 µm.

8. However, the present application is not directed to compositions manufactured by conventional granulation processes. The present application describes compositions processed under conditions wherein the drug and the alkaline substance is being contacted with an aqueous medium. This step is included in conventional granulation processes. However, according to the present invention, the mean particle size of the initial mixtures of the drug and alkaline substance should only increase within a narrow range upon being exposed to aqueous medium and dried. The increase in the mean particle size should be less than 100% in relation to the starting point. Furthermore, the overall particle size of the particulate composition before being exposed to aqueous solution and dried should be rather small in that the powder before being contacted with water should be such that at least 90% w/w of the particles passes through sieve 180 µm. After being contacted with an aqueous medium to form a particulate composition the particle size should be such that at least 50% w/w of the particles passes through sieve 180 µm.

9. I firmly believe that Masami et al failed to recognise some problems with the compositions processed by conventional granulation in that the process of enlarging the particle sizes by granulation (formation of aggregates) leads to poorer dissolution rates.

10. Under my supervision experiments have been carried out, which demonstrate that upon manufacturing a composition based on a particulate composition with enlarged particle sizes such as Masami et al., the release of NSAID from such a composition is not fast, but about 38% within 20 minutes of dissolution testing in 0.07 M hydrochloric acid. See data enclosed in Appendix A I wish to note that the particulate composition in this example was fractionated in a Retsch sieving apparatus with a lower screen of 0.5 mm and an upper screen of 0.8 mm, upon where particles in the size range of 500 to 800 µm is selected. This size range is in agreement with the upper limit defined in Masami et al.

11. It is my conclusion that compositions of Masami et al, which are based on particulate compositions with particle size of 800 µm or less, is not likely to result in quick release of the drug substance such that at least 50% of the drug substance is dissolved within 20 minutes of dissolution testing.

12. According to the present invention the step of contacting an alkaline substance with the active ingredient in an aqueous medium is also an essential element of the invention. However, on the basis of my experimental work, I am convinced that the step of including an alkaline substance in contact with the active ingredient may not inherently result in

the quick release of an NSAID upon dissolving the composition in gastric fluid. According to my understanding, the quick release is not just a matter of including an alkaline substance in the composition. The particle size of the particulate composition, wherein the active ingredient and the alkaline substance is in contact with each other, is an essential feature. Therefore, in order to ensure quick release (50% dissolved within 20 minutes of dissolution testing in gastric fluid) the particle size of the particulate composition that has been contacted with water should be such that at least 50% of the particles has a particle size of less than 180 μm.

13. As can be seen from examples 6 and 9 in the present application, the release rate from the composition depends on the particle size of the final particulate composition comprising the active ingredient and the alkaline substance after being contacted with aqueous solution and dried. Example 6 demonstrates the effect of increasing the particle size of the particulate composition. Even a slightly change in the mean particle size below or above 212 μm markedly affects the dissolution rate. For example, a tablet composition based on a particulate composition with a mean particle size less than 212 μm results in 93.1% dissolved NSAID after 20 minutes dissolution testing. Conversely, a tablet based on particulate composition with a mean particle size above 212 μm results in 85.4% dissolved NSAID after 20 minutes dissolution testing. Thus, upon decreasing the mean particle size of the particulate composition the dissolution rate becomes markedly faster. From example 9 it can be seen that in the case wherein about 60% of the particulate composition has a particle size less than 180 μm, the amount of dissolved NSAID within the first 20 minutes of dissolution testing is no more than 65.8 %.

14. I wish to note that the particle sizes of the particulate composition in examples 6 and 9 are well below the particle sizes of the particulate compositions of Masami et al. As stated, the compositions based on a particulate composition with higher particle sizes such that up to 800 μm will not lead to fast dissolution of the NSAID drugs.

15. I solved the problem seen with compositions of Masami et al by selecting significant lower particle sizes of that particulate composition, which subsequently may be compressed into tablets or filled into capsules or the like.

16. In light of the above-mentioned items 1 to 14, I firmly believe that the present invention contributes considerable to the art in that it is not obvious to the skilled person that smaller particle sizes may result in improved release rate, while still achieving oral dosage form with good mechanical resistance.

19 dec. 2002

Date:

Poul Bertelsen

Appendix A

Preparation of particulate composition with particle size of about 500 to 800 nm

Batch No. 19029835 was prepared.

Lornoxicam particulate composition was prepared using the following ingredients.

	Ingredients:	Amount (g)
I	Lornoxicam	7.5
II	Sodium bicarbonate	37.7
III	Cellulose, microcrystalline	90.4
IV	Dibasic Calcium Phosphate, Anhydrous	104.1
V	Low-substituted Hydroxypropyl Cellulose	45.3
VI	Hydroxypropylcellulose	15
VII	Purified water	115.8
VIII	Ethanol 99.9 %	38.7

The ingredients II to IV were mixed in a Moulinex laboratory size mixer and mixed for 5 min. To 100 g of this mixture ingredient I was added and mixed in a cubus mixer for 5 min. The resulting mass was screened through a 0.5 mm screen and returned to the Moulinex mixer and mixed for further 6 min. A premixed mixture of ingredient VII and VIII was added to the powder mixture and massed for 6 min.

The resulting mass was extruded in a Nica E 140 extruder with a screen size of 0.6 mm. The extrudate was spheronized in a laboratory size spheronizer at a rotation speed of 700 rpm for 4 min. The particulate composition thus produced were dried in a laboratory size fluid bed dryer with an inlet temperature of approximately 400 °C, and the drying process was continued until the outlet temperature has reached approximately 300 °C. The total drying time was approximately 25 min.

The dried particulate composition was fractionated in a Retsch sieving apparatus with a lower screen of 0.5 mm and an upper screen of 0.8 mm, thereby selecting particles in the range of 500 to 800 nm.

The release of lornoxicam from the pellet cores was determined by dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
After 1h	37.8

PHARMACEUTICAL DOSAGE FORMS

Tablets

SECOND EDITION, REVISED AND EXPANDED

In Three Volumes
VOLUME 1

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heating and cooling, a vacuum take-off, and a liquid dispersion bar through which a liquid binder can be added. As the blender rotates, liquid is sprayed into the powder charge through the rotating liquid dispersion bar, located concentric to the trunnion axis. The bar's dog-eared blades, rotating at 3300 rpm, aerates the powder to increase the speed and thoroughness of the blend. Granulation can be controlled by the rate of binder addition through the dispersion bar. After heating, the liquid of the binder is removed under reduced pressure. Mixing, granulating, heating, cooling, and removal of excess liquid are carried out in a continuous operation in an enclosed system, thereby protecting the contents from contamination and the adjacent area from contamination by the contents. Once the granulation process is completed, the remaining excipients can be added and blended by the simple rotating action of the blender. This unit is also known as a liquid-solids processor.

IV. GRANULATION

Most powders cannot be compressed directly into tablets because (a) they lack the proper characteristics of binding or bonding together into a compact entity and (b) they do not ordinarily possess the lubricating and disintegrating properties required for tableting. For these reasons, drugs must first be pretreated, either alone or in combination with a filler, to form granules that lend themselves to tableting. This process is known as granulation.

Granulation is any process of size enlargement whereby small particles are gathered together into larger, permanent aggregates [22] to render them into a free-flowing state similar to that of dry sand.

Size enlargement, also called agglomeration, is accomplished by some method of agitation in mixing equipment or by compaction, extrusions or globulation as described in the previous section on unit operations [4,23, 24].

The reasons for granulation as listed by Record [23] are to:

1. Render the material free flowing
2. Densify materials
3. Prepare uniform mixtures that do not separate
4. Improve the compression characteristics of the drug
5. Control the rate of drug release
6. Facilitate metering or volume dispensing
7. Reduce dust
8. Improve the appearance of the tablet

Because of the many possible approaches to granulation, selection of a method is of prime importance to the formulator.

A. Wet Granulation

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. This process has been extensively reviewed by Record [23], Kristensen and Schaefer [26], and Capes [27].